Amendments to the Specification

Please make the following amendments to the specification. Each amendment is listed first in a table, then in paragraph form. In the table, "Location" refers to the page and line number in the published application PCT/US2004/015786 (Publication No. WO 2004/103404 A1). Each amendment corresponds to a typographical error in the original application. Thus, no new matter is added by the amendments made herein.

Location	Currently reads	Should read
Page 2, line 18	present	present invention
Page 7, line 29	Burkift's	Burkitt's
Page 12, line 33	FcγRIIIbinding	FcγRIII binding
Page 13, line 22	Acqua	Dall'Acqua
Page 13, line 25	Acqua	Dall'Acqua
Page 14, line 7	N-aceylgalactosamine	N-acetylgalactosamine
Page 16, line 9	DPI7/21-2	DP7/21-2
Page 17, line 33	1, 4, and 6	1, 4, and 5
Page 20, line 5	42 C	42°C
Page 20, line 10	42 C	42°C
Page 20, line 15	42 C	42°C
Page 20, line 17	42 C	42°C
Page 20, line 19	42 C	42°C
Page 23, line 16	lyphoma	lymphoma
Page 24, line 14	present	present invention
Page 28, line 10	Kunkel et al., (1987)	Kunkel (1985)
Page 34, line 11	Bell	Cousens
Page 34, line 11	Schaffner	Koszinowski
Page 34, line 31	continues	continuous
Page 35, line 3	enitirities	entireties
Page 37, line 11	Burkift's	Burkitt's
Page 37, line 17	macroglobulianemia	macroglobulinemia
Page 37, line 22	myelemas	myelomas
Page 37, line 27	myelema	myeloma
Page 38, line 3	Castleman	Castleman's
Page 48, line 21	San die [Acs	San Diego [ACS
Page 48, line 26	periplamic	periplasmic
Page 50, line 26	Fluoresence	Fluorescence

Below, each amendment is shown in paragraph form. The incorrect phrase is lined through, and the corrected version is bolded and underlined. Page and line numbers indicate the location of the paragraph in the published application, PCT/US2004/015786 (Publication No. WO 2004/103404 A1).

At Page 2, lines 17-22, insert the following replacement paragraph:

The present invention provides CD20 binding molecules and nucleic acid sequences encoding CD20 binding molecules. In particular, the ~~present~~ **present invention** provides CD20 binding molecules with a high binding affinity, and a low dissociation rate, with regard to human CD20. Preferably, the CD20 binding molecules of the present invention comprise light and/or heavy chain variable regions with fully human frameworks (e.g. human germline frameworks).

At Page 7, lines 14-30, insert the following replacement paragraph:

In some embodiments, the present invention provides methods of treating B cell lymphoma comprising: a) providing; i) a subject, and ii) a composition, wherein the composition comprises a CD20 binding molecule of the present invention; and b) administering the composition to the subject. In other embodiments, the present invention provides methods of treating a disease comprising: a) providing; i) a subject with symptoms of the disease, and ii) a composition, wherein the composition comprises the CD20 binding molecules of the present invention; and b) administering the composition to the subject such that the symptoms are reduced or eliminated. In particular embodiments, the disease is selected from the group consisting of: relapsed Hodgkin's disease, resistant Hodgkin's disease high grade, low grade and intermediate grade non-Hodgkin's lymphomas (NHLs), B cell chronic lymphocytic leukemia (B-CLL), lymphoplasmacytoid lymphoma (LPL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large cell lymphoma (DLCL), Burkitt's lymphoma (BL), AIDS-related lymphomas, monocytic B cell lymphoma, angioimmunoblastic lymphoadenopathy, small lymphocytic; follicular, diffuse large cell; diffuse small cleaved cell; large cell immunoblastic lymphoblastoma; small, non-cleaved; ~~Burkift's~~ **Burkitt's** and non-Burkitt's; follicular, predominantly large cell; follicular, predominantly small cleaved cell; and follicular, mixed small cleaved and large cell lymphomas.

At Page 12, lines 17-22, insert the following replacement paragraph:

As disclosed above, one can design an Fc region of a CD20 binding molecule with altered effector function, e.g., by modifying C1q binding and/or FcγR binding and thereby changing CDC activity and/or ADCC activity. For example, one can generate a variant Fc region of a CD20 binding molecule with improved C1q binding and improved ~~FcγRIIIbinding~~ **FcγRIII binding** (e.g., having both improved ADCC activity and improved CDC activity).

At Page 13, lines 5-30, insert the following replacement paragraph:

Fc mutations can also be introduced in the CD20 binding molecules of the present invention to alter their interaction with the neonatal Fc receptor (FcRn) and improve their pharmacokinetic properties. Several experiments suggest that the interaction between the Fc region of an antibody and the FcRn plays a role in the persistence of immunoglobulins in serum. For instance, an unusually short serum half-life is observed for IgG molecules in mice that lack a functional FcRn. Fc mutations that improve binding to the FcRn appear to prolong serum half-life and, conversely, mutations in the rat FcRn that result in tighter IgG binding also improve serum half-life. A collection of human Fc variants with improved binding to the FcRn has also been described (Shields et al., (2001) High resolution mapping of the binding site on human IgGI for FcγRI, FcγR11, FcγRIII, and FcRn and design of IgG1 variants with improved binding to the FcγR, J. Biol. Chem. 276:6591-6604). It has been reported that the increased binding affinity of IgG molecules for the FcRn observed at low pH (e.g., during pinocytosis or fluid phase endocytosis of IgG molecules from serum) impacts serum half-life (Ghetie et al., (1997) Increasing the serum persistence of an IgG fragment by random mutagenesis, Nat. Biotechnol. 15:637-640; Medesan et al., (1998) Comparative studies of rat IgG to further delineate the Fc:FcRn interaction site. Eur. J. Immunol. 28:2092-2100; Kim et al., (1999) Mapping the site on human IgG for binding of the MHC class I-related receptor, FcRn, Eur. J. Immunol. 29:2819-2825; ~~Acqua~~ **Dall'Acqua** et al., (2002) Increasing the affinity of a human IgGI for the neonatal Fc receptor: biological consequences, J. Immunol. 169:5171-5180). However, mutations that increase binding at high pH appear to adversely affect serum half-life (~~Acqua~~ **Dall'Acqua** et al., (2002) Increasing the affinity of a human IgG1 for the neonatal Fc receptor: biological consequences, J. Immunol. 169:5171-5180). All of the articles above are herein incorporated by reference. Therefore, Fc mutations could be introduced in the CD20 binding molecules of the present invention in order to increase their affinity for the FcRn at low pH but maintain or decrease their affinity for the FcRn at higher pH.

At Page 13, line 31 through page 14, line 9, insert the following replacement paragraph:

Another type of amino acid substitution serves to alter the glycosylation pattern of the Fc region of a CD20 binding molecule. This may be achieved, for example, by deleting one or more glycosylation site(s) found in the polypeptide, and/or adding one or more glycosylation sites that are not present in the polypeptide. Glycosylation of an Fc region is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an

asparagine residue. The peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars ~~N-acetylgalactosamine~~ **N-acetylgalactosamine**, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

At Page 16, lines 5-11, insert the following replacement paragraph:

Figure 9A shows the amino acid sequence of the human heavy chain framework region VHI DP7/21-2 with interspersed CDRs. The four framework sub-regions are labeled as follows: FRH1 (SEQ ID NO:95), FRH2 (SEQ ID NO:96), FRH3 (SEQ ID NO:97), and FRH4 (SEQ ID NO:98). Figure 9B shows the nucleic acid sequence of the human heavy chain framework region VHI ~~DPI7/21-2~~ **DP7/21-2** with interspersed CDRs. The four framework sub-regions are labeled as follows: FRH1 (SEQ ID NO:99), FRH2 (SEQ ID NO:100), FRH3 (SEQ ID NO:101), and FRH4 (SEQ ID NO:102).

At Page 17, line 31 through page 18, line 6, insert the following replacement paragraph:

As used herein, the term "framework" refers to the residues of the variable region other than the CDR residues as defined herein. There are four separate framework sub-regions that make up the framework: FR1, FR2, FR3, and FR4 (See Figures ~~1, 4, and 6~~ **1, 4, and 5**). In order to indicate if the framework sub-region is in the light or heavy chain variable region, an "L" or "H" maybe added to the sub-region abbreviation (e.g., "FRL1" indicates framework sub-region 1 of the light chain variable region). Unless specified, the numbering of framework residues is according to Kabat. It is noted that, in certain embodiments, the CD20 binding molecules of the present invention may have less than a complete framework (e.g. the CD20 binding molecule may have a portion of a framework that only contains one or more of the four sub-regions).

At Page 20, lines 4-20, insert the following replacement paragraph:

"High stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at ~~42 C~~ **42°C** in a solution consisting of 5X SSPE (43.8 g/l NaCl, 6.9 g/l NaH_2PO_4 H_2O and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.5% SDS, 5X Denhardt's reagent [50X Denhardt's contains per 500 ml: 5 g Ficoll

(Type 400, Pharmacia), 5 g BSA (Fraction V; Sigma)] and 100 μg/ml denatured salmon sperm DNA, followed by washing in a solution comprising 0.1X SSPE, 1.0% SDS at ~~42 C~~ **42°C** when a probe of about 500 nucleotides in length is employed.

"Medium stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 42°C in a solution consisting of 5X SSPE, 0.5% SDS, 5X Denhardt's reagent and 100 μg/ml denatured salmon sperm DNA, followed by washing in a solution comprising 1.0X SSPE, 1.0% SDS at ~~42 C~~ **42°C** when a probe of about 500 nucleotides in length is employed.

"Low stringency conditions" comprise conditions equivalent to binding or hybridization at ~~42 C~~ **42°C** in a solution consisting of 5X SSPE, 0.1% SDS, 5X Denhardt's reagent and 100 g/ml denatured salmon sperm DNA, followed by washing in a solution comprising 5X SSPE, 0.1% SDS at ~~42 C~~ **42°C** when a probe of about 500 nucleotides in length is employed.

At Page 23, lines 4-16, insert the following replacement paragraph:

The term "human CD20" (abbreviated herein as hCD20), as used herein, is intended to refer to the human B lymphocyte-restricted differentiation antigen (also known as Bp35). CD20 is expressed during early pre-B cell development and remains until plasma cell differentiation. The CD20 molecule may regulate a step in the activation process which is required for cell cycle initiation and differentiation, and is usually expressed at very high levels on neoplastic B cells. CD20 is present on both "normal" B cell as well as "malignant" B cells (i.e. those B cells whose unabated proliferation can lead to B cell ~~lyphoma~~ **lymphoma**).

At Page 24, lines 13-20, insert the following replacement paragraph:

The present invention provides CD20 binding molecules and nucleic acid sequences encoding CD20 binding molecules. In particular, the ~~present~~ **present invention** provides CD20 binding molecules with a high binding affinity, and a low dissociation rate, with regard to human CD20. Preferably, the CD20 binding molecules of the present invention comprise light and/or heavy chain variable regions with fully human frameworks (e.g. human germline frameworks). The description of the invention is divided into the following sections below for convenience: I. CD20 Binding Molecules; II. Generating CD20 Binding Molecules; III. Therapeutic Formulations and Uses; and IV. Additional CD20 Binding Molecule Uses.

At Page 27, line 4 through page 28, line 11, insert the following replacement paragraph:

The present invention also provides sequences that are substantially the same as the CDR sequences (both amino acid and nucleic acid) shown in the above Tables. For example, one or two amino acid may be changed in the sequences shown in the Tables. Also for example, a number of nucleotide bases may be changed in the sequences shown in the Tables. Changes to the amino acid sequence may be generated by changing the nucleic acid sequence encoding the amino acid sequence. A nucleic acid sequence encoding a variant of a given CDR may be prepared by methods known in the art using the guidance of the present specification for particular sequences. These methods include, but are not limited to, preparation by site-directed (or oligonucleotide-mediated) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared nucleic acid encoding the CDR. Site-directed mutagenesis is a preferred method for preparing substitution variants. This technique is well known in the art (see, e.g., Carter et al., (1985) Nucleic Acids Res. 13: 4431-4443 and ~~Kunkel et. al., (1987)~~ **Kunkel (1985)** Proc. Natl. Acad. Sci. USA 82: 488-492, both of which are hereby incorporated by reference).

At Page 33, line 29 through page 34, line 12, insert the following replacement paragraph:

In addition to the antibody chain genes, the recombinant expression vectors of the invention may carry regulatory sequences that control the expression of the antibody chain genes in a host cell. The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals) that control the transcription or translation of the antibody chain genes. Such regulatory sequences are described, for example, in Goeddel; Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, Calif. (1990), herein incorporated by reference. It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV) (such as the CMV promoter/enhancer), Simian Virus 40 (SV40) (such as the SV40 promoter/enhancer), adenovirus, (e.g., the adenovirus major late promoter (AdMLP)) and polyoma virus. For further description of viral regulatory elements, and sequences thereof, see e.g., U.S. Pat. No. 5,168,062 by Stinski, U.S. Pat. No. 4,510,245 by ~~Bell~~ **Cousens** et al. and U.S. Pat. No. 4,968,615 by ~~Schaffner~~ **Koszinowski** et al., all of which are herein incorporated by reference.

At Page 34, line 29 through page 35, line 3, insert the following replacement paragraph:

In certain embodiments, the expression vector used to express the CD20 binding molecules of the present invention are viral vectors, such as retro-viral vectors. Such viral vectors may be employed to generate stably transduced cell lines (e.g. for a ~~continues~~ **continuous** source of the CD20 binding molecules). In some embodiments, the GPEX gene product expression technology (from Gala Design, Inc., Middleton, WI) is employed to generate CD20 binding molecules (and stable cell lines expressing the CD20 binding molecules). In particular embodiments, the expression technology described in WO0202783 and WO0202738 to Bleck et al. (both of which are herein incorporated by reference in their ~~enitirities~~ **entireties**) is employed.

At Page 37, line 3 through page 38, line 8, insert the following replacement paragraph:

In certain embodiments, the disease treated is Non-Hodgkin's lymphoma (NHL). In some embodiments, the disease is selected from relapsed Hodgkin's disease, resistant Hodgkin's disease high grade, low grade and intermediate grade non-Hodgkin's lymphomas (NHLs), B cell chronic lymphocytic leukemia (B-CLL), lymphoplasmacytoid lymphoma (LPL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large cell lymphoma (DLCL), Burkitt's lymphoma (BL), AIDS-related lymphomas, monocytic B cell lymphoma, angioimmunoblastic lymphoadenopathy, small lymphocytic; follicular, diffuse large cell; diffuse small cleaved cell; large cell immunoblastic lymphoblastoma; small, non-cleaved; ~~Burkift's~~ **Burkitt's** and non-Burkitt's; follicular, predominantly large cell; follicular, predominantly small cleaved cell; follicular, mixed small cleaved and large cell lymphomas, and systemic lupus erythematosus (SLE). In particular embodiments, the disease treated is Waldenstrom's Macroglobulinemia (WM) or Chronic Lymphocytic Leukemia (CLL).

In some embodiments, the CD20 binding molecules of the present invention are used for treatment of diseases wherein depletion of CD20+ cells is therapeutically beneficial, such as Waldenstrom's ~~macroglobulianemia~~ **macroglobulinemia**, multiple myeloma, plasma cell dyscrasias, chronic lymphocytic leukemia, treatment of transplant, hairy cell leukemia, ITP, Epstein Barr virus lymphomas after stem cell transplant, and Kidney transplant, see U.S. Pat. Pub. 20020128448, herein incorporated by reference. In other embodiments, the CD20 binding molecules of the present invention are used for the treatment of a disease selected from the group consisting of B cell lymphomas, leukemias, ~~myelemas~~ **myelomas**, autoimmune disease,

transplant, graft-vs-host disease, infectious diseases involving B cells, lymphoproliferation diseases, and treatment of any disease or condition wherein suppression of B cell activity and/or humoral immunity is desirably suppressed. In certain embodiments, the CD20 binding molecules of the present invention are used for the treatment of a disease selected from the group consisting of B cell lymphomas, leukemia, ~~myeloma~~ **myeloma**, transplant, graft-vs-host disease, autoimmune disease, lymphoproliferation conditions, and other treatment diseases and conditions wherein the inhibition of humoral immunity, B cell function, and/or proliferation, is therapeutically beneficial. In further embodiments, the CD20 binding molecules of the present invention are used for the treatment of B-ALL, Hairy cell leukemia, Multiple myeloma, Richter Syndrome, Acquired Factor VIII inhibitors, Antiphospholipid syndrome, Autoimmune hemolytic anemia, Autoimmune thrombocytopenia, Bullous pemphigoid, Cold hemagglutinin disease, Evan's Syndrome, Goodpasture's syndrome, Idiopathic membranous nephropathy, Idiopathic thrombocytopenic purpura, IgM associated polyneuropathy, Kaposi sarcoma-associated herpesvirus (KSHV)-related multicentric ~~Castleman~~ **Castleman's** disease (MCD), Myasthenia gravis, Pemphigus vulgaris, Primary biliary cirrhosis, Pure red cell aplasia, Rheumatoid arthritis, Sjogren's Syndrome, Systemic immune complex vasculitis, Systemic lupus erythematosus, Type II mixed cryoglobulinemia, Wegener's granulomatosis, Allograft rejection, Post-transplant lymphoproliferative disease, or Purging of stem cells for bone marrow transplantation.

At Page 48, line 9 through page 49, line 2, insert the following replacement paragraph:

In order to express the anti-CD20 binding molecules in this example (as Fabs or IgGs), procedures known in the art may be used. For example, the eleven CD20 binding molecules in this example can be expressed, as Fabs or IgG's, in mammalian expression systems (or bacterial, fungal and plant expression systems) using either a single vector or double vector system. In a single vector system both heavy and light chains are manufactured or cloned within an expression cassette, which contains all required regulatory elements for expression. A double vector system simply has these two expression cassettes in separate plasmids. Either the single, or combined plasmids in the double vector system, may be transfected into a host cell line such as Chinese Hamster Ovary (CHO) cells or the retinal cell line PerC6, selected for, expanded and cultured to express the Fab or IgG proteins as is known in the art (see Antibody Expression and Engineering: Developed from a Symposium Sponsored by the Division of Biochemical Technology at the 207th National Meeting of the American Chemical Society, ~~San die [Acs~~ **San Diego [ACS** Symposium Series, 604]).

Fabs may also be expressed in a bacterial expression system, as this is less time consuming and less expensive than mammalian systems. Here Fabs can be inserted and expressed within a M13 viral expression system. Bacterial expressed Fabs are secreted and also accumulate within the ~~periplamic~~ **periplasmic** space between the bacterial cell wall and its cell membrane. The Fab can be released from this periplasmic space by a number of techniques including hypotonic shock and freeze thaw procedures common in the art. Fab's can also be generated from intact IgG by proteolytic cleavage using a protease such as papain. The Fab portion of the cleavage product can then be purified away from the Fc portion of the cleavage product. Fabs and IgG's can be purified with any variety of chromatographic and specific adsorption techniques that are also known in the art (see Antibodies: A Laboratory Manual, by Ed Harlow (Editor), David Lane (Editor), Cold Spring Harbor Press). For example IgG's can be easily purified from cellular supernatants by specific binding using rProtein A affinity chromatography followed by Mono S cation exchange chromatography.

At Page 50, lines 16-28, insert the following replacement paragraph:

Peripheral blood mononuclear cells (PBMC) were isolated from normal human blood by flotation on Ficol-Hypaque (Sigma-1077). Cells were counted and resuspended in PBS + 1% BSA to give 2-5x10^6 cells/ml. One hundred microliters of diluted cells were dispensed into polystyrene tubes (Falcon #2058) and anti-CD20 Fab antibodies diluted in PBS + 1% BSA were added. Tubes were incubated 1 hour at room temperature. Four milliliters of PBS + 1% BSA were added to each tube and the tubes were centrifuged at 300 xG for 10 minutes. The supernatant was removed and the cells resuspended in 100 µl PBS + 1% BSA. Anti-Penta-His AlexaFluor 488 conjugate (Qiagen #35310), 2 µl per tube, was added, the tubes were mixed and incubated for 1 hour in the dark at room temperature. Samples were washed as previously described. The supernatant was removed and the cells resuspended in PBS + 1% BSA+ 2 µg/ml Propidium iodide. ~~Fluoresence~~ **Fluorescence** was analyzed on a Becton Dickinson FACScan or FACSort flow cytometer and data analyzed using Cell Quest (Becton Dickinson) or WinMDI software.

Additionally, please insert the following cross-reference into the specification.

At page 1, line 3:

This is the national phase application, under 35 U.S.C. § 371, for PCT/US2004/015786, which claims the benefit of 60/471,958, filed 20 May 2003, which is incorporated herein by reference.